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Diastereoselective homoallylation and bis-homoallylation of *N-tert*-butanesulfinyl imines with organomagnesium compounds

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Dedicated to Prof. Miguel Yus on the occasion of his 70th birthday and for his contribution as Editor-in-Chief of Letters in Organic Chemistry

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Abstract: The addition of but-3-enylmagnesium bromide and pent-4-enylmagnesium bromide to *N-tert*-butanesulfinyl aldimines in toluene as solvent proceeds with high diastereoselectivity to yield the corresponding products of homoallylation and bis-homoallylation, respectively. The reactions are diastereoselective, and the configuration of the sulfur atom of the sulfinyl group determined the stereochemical outcome. The reaction products are aminoalkene derivatives of potential synthetic interest as precursors of nitrogen containing heterocycles.

Keywords: Homoallylation; bis-homoallylation, diastereoselective addition; *N-tert*-butanesulfinyl imines; Grignard reagents.

1. INTRODUCTION

A huge number of organic compounds displaying biological activities with potential applications in the drug industry bear the amine functionality, including natural products [1]. In addition, the nitrogen atom is bonded to a stereogenic center in many of these amines. That is the reason why the development of synthetic methodologies which allow an easy access to aminated compounds in an efficient, reliable, simple, and more importantly, stereoselective manner, is of great interest. Among these methodologies, the addition of organometallics to imines has attracted much attention recently. When these transformations involve an allylic organometallic compound, the resulting homoallylamine derivatives are valuable building blocks, because along with the carbon stereogenic centre bonded to the nitrogen atom, the double bond of the allylic moiety can participate in a number of further synthetically useful transformations: dihydroxylation, epoxidation, hydroformylation, hydrogenation, hydration, olefin metathesis, ozonolysis, etc [2].

The stereoselective allylation can be performed under the influence of catalytic amounts of chiral Lewis acids or bases [3], although there are more efficient and practical protocols using stoichiometric amounts of chiral reagents [4], such as imines bearing a chiral auxiliary. Because of that, chiral *N*- *tert*-butanesulfinyl imines have found high applicability in synthesis [5], mostly due to the easy preparation and availability of both enantiomers [6]. The *tert*-butanesulfinyl group can be removed easily under acidic conditions leading to free amines [7] and also, procedures to recycle the chiral *tert*-butanesulfinamide unit have been reported [8]. With regards to this, we have described the stereoselective synthesis of homoallylic amine derivatives by allylation with allyl indium species of *N-tert*-butanesulfinyl aldimines [9] and ketimines [10], and the α-aminoallylation of aldehydes with chiral *tert*-butanesulfinamide, allyl bromides, and indium, as well [11].

Continuing our interest in the study of the nucleophilic additions to these chiral sulfinyl imines and the influence of the *tert*-butanesulfinyl group on the stereochemical outcome of these reactions, we herein report our first approach to the homoallylation and bis-homoallylation of *N-tert*-butanesulfinyl imines using organomagnesium compounds as nucleophiles. To the best of our knowledge, the synthesis of these *N-tert*-butasulfinyl alkenamines was previously provided by Fustero and del Pozo [12] involving the addition of organomagnesium compounds to the imines derived from pent-4-enal and hex-5-enal (Scheme 1). A similar strategy was employed by the group of Stahl in their study of the stereoselective synthesis of *cis*-2,5-disubstituted pyrrolidines [13]. Since the addition of Grignard reagents to these chiral sulfinyl imines proceeds in a diastereoselective manner, the two possible diastereoisomers are accessible by applying either strategy (previously reported and the one presented in this work), both of which are complementary in this way (Scheme 1).

2. RESULTS AND DISCUSSION

The starting sulfinylimines **1** were prepared according to the standard procedure described in the literature, by reaction of commercially available (*R*)-*tert*-butanesulfinamide with the corresponding aldehyde in the presence of titanium

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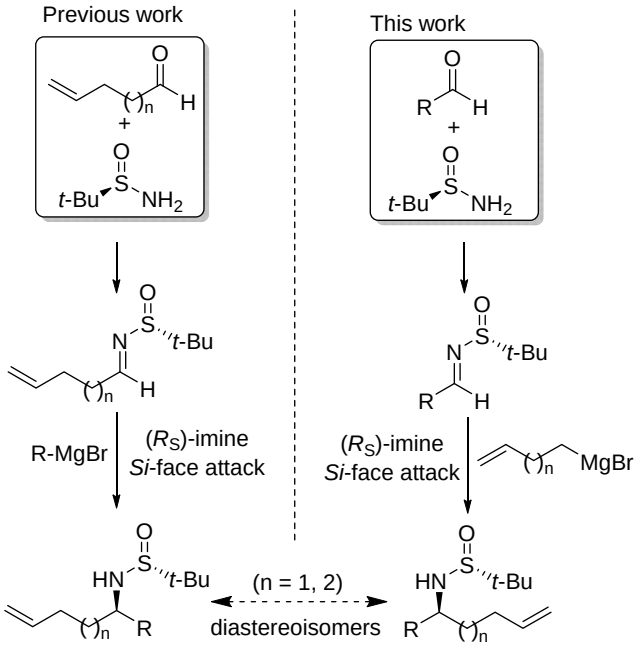
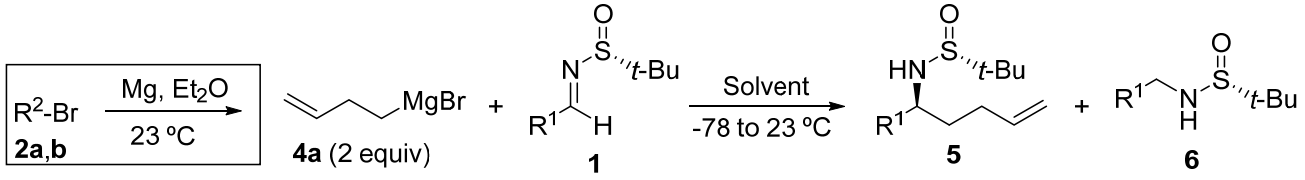


Scheme 1. Diastereoselective addition of organomagnesium compounds to *N-tert*-butanesulfinyl imines.

tetraethoxide in THF [14].

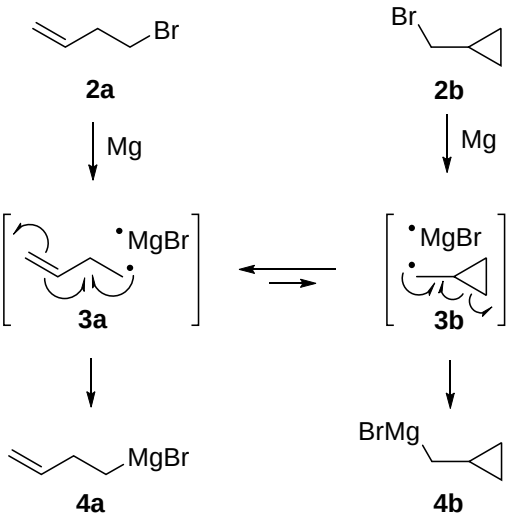
In order to determine the best reaction conditions for the addition of but-3-enylmagnesium bromide (**4a**) to chiral *N-tert*-butanesulfinyl imines **1**, we took imines **1a** and **1b**, derived from benzaldehyde and 3-phenylpropanal, respectively, as model compounds. The first diastereoselective addition of Grignard reagents to *N-tert*-butanesulfinyl aldimines **1** was reported by Ellman and co-workers [15]. They found that the best results were obtained working in no coordinating solvents, such as dichloromethane [7]. Taking into account the configuration of the major resulting diastereoisomers, they proposed a chelated transition state, which was also consistent with the observed solvent effect, because competitive coordination of ethereal solvents, such as THF, would interfere with the formation of the six-membered-ring transition state. According to this model, the attack of the organomagnesium compound occurred on the *Si* face of the imine with *R* configuration at the sulfur atom. For that reason, we studied first the addition of 1M solution of but-3-enylmagnesium bromide (**4a**) in ether to the imine **1a** in different solvents. The addition was carried out at -78 °C, and after that, the reaction mixture was allowed to reach room temperature. The highest diastereoselectivity was obtained performing the reaction in toluene (96:4 dr, Table 1, entry 4), although similar levels of diastereocontrol were achieved using dichloromethane (95:5 dr, Table 1, entry 3). Poorer results were obtained in diethyl ether (83:17 dr, Table 1, entry 2), and the lowest diastereoselectivity was reached in THF as solvent (Table 1, entry 1). We found that both 4-bromobut-1-ene (**2a**) and bromomethylcyclopropene (**2b**), upon reaction with magnesium in dry diethyl ether at 23 °C for 4 hours, led to but-3-enylmagnesium bromide (**4a**). Importantly, the reaction product resulting from the addition of cyclopropylmethylmagnesium bromide (**4b**) was never observed when bromomethylcyclopropene (**2b**) was used in these transformations as the precursor of the organomagnesium compound (Table 1, entries 5-8). This can be explain by considering that cyclopropylmethyl radical (**3b**) initially formed from **2b**, isomerized to but-3-enyl radical (**3a**), which is the direct precursor of **4a** (Scheme 2) [16]. Similar levels of diastereocontrol were also found in

Table 1. Optimization of the reaction conditions



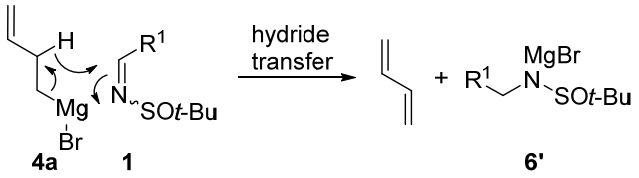
	Starting imine		Starting Bromide			Products (%)[a]		
Entry	No.	R^1	No.	R^2	Solvent	**5**[b]	**6**	**1**
1	**1a**	Ph	**2a**	CH_2=$CHCH_2CH_2$	THF	90 (41:59)	2	8
2	**1a**	Ph	**2a**	CH_2=$CHCH_2CH_2$	Et_2O	43 (83:17)	6	51
3	**1a**	Ph	**2a**	CH_2=$CHCH_2CH_2$	CH_2Cl_2	52 (95:5)	16	29
4	**1a**	Ph	**2a**	CH_2=$CHCH_2CH_2$	$PhCH_3$	75 (96:4)	17	8
5	**1a**	Ph	**2b**	*c*-$PrCH_2$	THF	98 (62:38)	2	0
6	**1a**	Ph	**2b**	*c*-$PrCH_2$	Et_2O	83 (83:17)	14	3
7	**1a**	Ph	**2b**	*c*-$PrCH_2$	CH_2Cl_2	74 (95:5)	20	5
8	**1a**	Ph	**2b**	*c*-$PrCH_2$	$PhCH_3$	43 (89:11)	10	47
9	**1b**	$Ph(CH_2)_2$	**2a**	CH_2=$CHCH_2CH_2$	CH_2Cl_2	80 (91:9)	10	10
10	**1b**	$Ph(CH_2)_2$	**2a**	CH_2=$CHCH_2CH_2$	$PhCH_3$	88 (93:7)	12	0
11	**1b**	$Ph(CH_2)_2$	**2b**	*c*-$PrCH_2$	CH_2Cl_2	91 (89:11)	9	0
12	**1b**	$Ph(CH_2)_2$	**2b**	*c*-$PrCH_2$	$PhCH_3$	91 (93:7)	9	0

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Diastereomeric ratio is given in parenthesis.



Scheme 2. Synthesis of but-3-enylmagnesium bromide (**4a**) from alkyl bromides **2a** and **2b**.

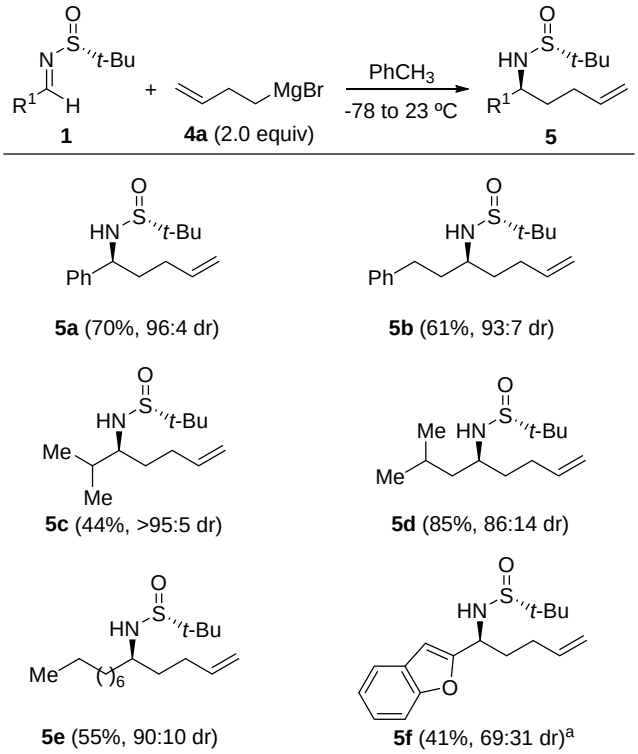
the reaction of the aliphatic imine derived from 3-phenylpropanal (**2a**), in dichloromethane and toluene, starting indepently from alkyl bromide **2a** or **2b**, in the preparation of the Grignard reagent **4a** (Table 1, entries 9-10). Variable amounts of *N-tert*-butanesulfinamides **6** were always obtained as side reaction products. They are formed through a competitive hydride transfer reaction, because of the formation of 1,3-butadiene (Scheme 3). Reaction products ratios were determined by ^{1}H-NMR analysis of the crude reaction mixtures through the comparison of the integrals of the *t*-Bu group.



Scheme 3. Reduction of *N-tert*-butanesulfinyl imines **1** with but-3-enylmagnesium bromide (**2a**) through a hydride transfer reaction.

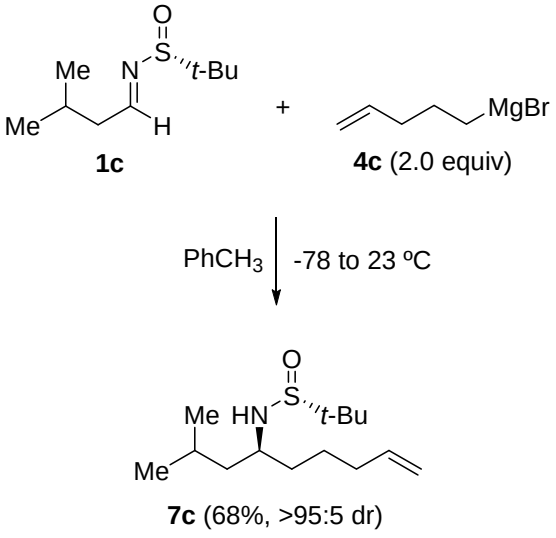
Next, we studied the homoallylation of different *N-tert*-butanesulfinyl imines **1**, using toluene as solvent and starting from 4-bromobut-1-ene (**2a**) as precursor of organomagnesium compound **4a**. The expected homoallylamine derivatives **5** were obtained in variable yields and diastereoselectivities (Scheme 4). The lowest diastereoselectivity was obtained for compound **5f** derived from the imine of 2-benzofurancarboxaldehyde (**1f**) and the highest yield for compound **5d**, which derived from the imine of isovaleraldehyde (**1d**, Scheme 4). Yields given on Scheme 4 refer to isolated yield of the major diastereoisomer after column chromatography purification.

Finally, bis-homoallylation of the imine **1c** derived from isovaleraldehyde was carried out applying this methodology. In this case, organomagnesium compound **4c** was prepared from 5-bromopent-1-ene. The expected product **7c** was obtained with high diastereoselectivity in



Scheme 4. Scope for formation of **5**. Isolated yields of the major diastereoiosmer after column chromatography purification are shown.[a] Minor diastereoisomer was isolated in 18% yield.

68% yield, after column chromatography purification (Scheme 5).



Scheme 5. Bis-homoallylation of *N-tert*-butanesulfinyl imine **1c** with pent-4-enylmagnesium bromide.

CONCLUSION

From the results shown here we conclude that the addition of but-3-enylmagnesium bromide and pent-4-enylmagnesium bromides to *N*-*tert*-butanesulfinyl aldimines takes place with high diastereoselectivity. Interestingly, the configuration of the newly created stereogenic centre is determined by the configuration of the sulfur atom of the *tert*-butanesulfinyl unit. Enantioenriched aminoalkene derivatives can be prepared following this methodology, these compounds being synthetic intermediates of wide applicability in the synthesis of nitrogen containing heterocycles.

CONFLIT OF INTEREST

The authors declare no conflict of interest.

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SUPPLEMENTARY MATERIALS

Experimental procedure and copies of ^{1}H and ^{13}C NMR spectra.

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